IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Spector, Lorraine
Avi ASHKENAZI, *et al.*	)	Art Unit: 1647
Application Serial No. 09/904,877	)	Confirmation No: 4450
Filed: July 12, 2001	)	Attorney's Docket No. 39780-1618 P2C27
For: **PRO326 POLYPEPTIDES**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On February 4, 2005, the Examiner made a final rejection to pending Claims 42-47 and 49-51. A Notice of Appeal was filed on August 3, 2005, and Appellants' Appeal Brief was filed on October 3, 2005. A revised Appeal Brief was filed January 6, 2006 and an Examiner's Answer was mailed on May 1, 2006.

The following constitutes the Appellants' Reply Brief in response to the Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

Arguments begin on page 2 of this paper.

ARGUMENTS

I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 42-47 and 49-51 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in his Answer, the Examiner cites the following arguments:

(1) "in brief....the assay is *not* by itself, accepted in the art as establishing that it is more likely than not that a compound is a proinflammatory molecule, rather all it establishes is that the molecule is toxic or irritating, and that substantial further experimentation, of the type found to be part of the invention itself, would be required to determine how to use the protein, and hence the claimed nucleic acids" (page 8, lines 1 through 5 of the Examiner's Answer).

(2) the Examiner says that the SVP (skin vascular permeability assay) is not indicative of utility for PRO326 "because it is merely what is commonly known as an immediate type hypersensitivity assay." The Examiner continues to refer to PRO326 as an irritant and not as a proinflammatory molecule and adds that "merely identifying an agent as a proinflammatory agent does not confer utility";

(3) (w)hat has *not* been shown is: (i)t has *not* been shown *if* **PRO326 is produced *by* the guinea pig**, nor under what conditions. It has *not* been shown what types of cells may have migrated to the wound response, a characterization that is shown to be standard in the art when using such an assay. It has *not* been shown that the expression profile of PRO326 is similar to any other protein, as was done by Rampart *et al.*- (reference submitted by Appellants with response of July 22, 2003). The Examiner adds that "appellants own argument shows how very preliminary the result is, and that **substantial further experimentation would be required** to determine a utility for PRO326" (italic emphasis in the original; bold emphasis added- (see Examiner's Answer).

Appellants disagree with each of the Examiner's arguments for the reasons detailed below.

First of all, Appellants respectfully remind the Examiner that an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "**unless there is a reason for one skilled in threat to question the objective truth of the statement of utility or its scope.**" (Emphasis added) *In re Langer*, 503 F.2d 1380,

1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." (Emphasis added) *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Appellant to provide rebuttal evidence. *Id.*

Arguments

The Examiner's arguments will be addressed in the order in which they are listed above.

Appellants have discussed throughout prosecution that PRO326 is not an irritant nor does it cause a hypersensitive reaction, as seen at least in their Appeal brief filed October 3, 2005 and further in their amended Appeal brief filed January 6, 2006. By definition, hypersensitive reactions need prior exposure to the antigen (or irritant) in question, in order to elicit an immune response. In this instance, the animal (guinea pig) in the SVP assay was not pre-exposed or sensitized to PRO326. Therefore, the Examiner's rejections based on "hypersensitive reactions" or "irritants" are inappropriate and do not apply in this instance.

The Examiner further questions **whether PRO326 is produced by guinea pigs**. Appellants submit, as stated clearly in the specification, that secretory polypeptides like PRO326 disclosed in the instant specification are **human** secretory proteins (see field of invention,

introduction, of the instant specification). Even considering arguendo, if there supposedly were regions of homology between human PRO326 in any guinea pig protein, which Appellants strongly do not concede to, such homologous regions, being self-antigens for the guinea pig, would not be expected to mount an immune/ inflammatory response to PRO326. Therefore, any rejection based on the notion that "PRO326 (maybe) produced by guinea pigs" is nonsensical and should not be applied in this instance. Appellants submit that the Examiner's conclusions that PRO326 is an "irritant" or causes "a hypersensitive reaction" has no logical basis, and stems from misconceptions regarding the field of inflammation. For these reasons alone, one skilled in the art would never conclude that PRO326 is an irritant or a self-antigen.

Instead, Appellants assertion of utility is based on the positive reaction in the SVP assay (Example 77 in the instant specification), which is well-known in the art as an assay for identifying inflammatory molecules. This point was discussed in detail in the Declaration by Dr. Sherman Fong, which further sets forth the state of the art in the field of inflammation as a whole, as it existed at the time of the instant filing, and also presents several exemplary references wherein assays similar to the SVP assay were used for identifying candidate inflammatory molecules. Thus, based on the knowledge known and available to one skilled in the art, a positive reaction for PRO326 in the SVP assay would undoubtedly be a showing that PRO326 is an inflammatory molecule, and further, one skilled in the art would find the Appellants' assertion that "PRO326 enhances or induces an immune response" credible.

The Examiner also inquires "**what types of cells may have migrated to the wound response**." Example 77 (page 210) which describes a dye-based proinflammatory cell infiltration assay clearly discloses inflammatory polypeptides as "**inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal" (page 210, lines 23-24 of the specification)**. Further, the types of cells migrating to the site of injection in response to inflammation were also well known in the art at the time of filing, as detailed in the Fong Declaration and demonstrated in the Exhibit B: "Regulation of Leukocyte movement" attached therein.

Appellants further note that the Examiner has failed to meet the initial evidentiary burden in making this rejection. The Utility standard (see above) clearly states that the Examiner **has the initial burden to offer evidence** to show that one of ordinary skill in the art would have a

legitimate basis for doubting the credibility of the data in Example 77 and for asserting utility based on their data. In fact, **the Examiner has not provided any evidence** such that one skilled in the art would doubt the credibility of the instantly claimed utility. The Examiner says on page 10, line 22-24 of the Examiner's Answer that "Appellants repeatedly argue that the Examiner has failed to cite evidence to support the finding of lack of utility. Specific evidence that PRO326 polypeptide is not a proinflammatory molecule **is neither required nor possible**, as the Examiner does not possess laboratory facilities. As set forth in the MPEP, a finding of lack of utility may be properly made if there is a scientific basis to doubt the assertion of utility." Appellants strongly disagree. While Appellants do not require the Examiner to cite "specific evidence for PRO326," they need the Examiner to provide evidence to show that one of ordinary skill in the art would have a legitimate basis for doubting the credibility of their data in Example 77. Surely the Examiner's counterargument does not meet the USPTO set utility standards. More importantly, as discussed above, the Examiner's rejections are based on several misconceptions of the field of inflammation and erroneous conclusions thereof. Accordingly, the burden to rebut the utility rejection has not properly shifted to the Appellants and a lack of utility rejection is inappropriate in this instance.

Yet, even without the Examiner having met this initial burden of offering countervailing evidence, that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence. Appellants provided the Rampart *et al.* (*Am J Pathol* **135(1)**:21-25 (1989)) reference (submitted by Appellants with response of July 22, 2003) that identified IL-8 using a rabbit skin neutrophil accumulation assay similar to the present SVP assay. Rampart *et al.* suggested the involvement of endogenous IL-8 in an acute phase inflammatory response of an animal to a microbial stimulus and further disclosed suggestive data supporting its involvement in psoriasis (see page 24, column 1, last paragraph). Further, the Fong Declaration details the state of the art of inflammation and provides art accepted examples of the usefulness for proinflammatory molecules. Therefore, it is more likely than not that those skilled in the art, to a reasonable probability, would believe that the claimed polypeptide is useful because it encodes a proinflammatory molecule, and therefore, is useful for generating antagonistic molecules, like antibodies, against PRO326, to treat diseased conditions involving inflammation.

But the Examiner asserts that "substantial further experimentation would be required to determine a utility for PRO326."

Appellants respectfully disagree and submit that "(t)he mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility." M.P.E.P. §2107.01 III cites *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q. 2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law....necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is readily to be administered to humans." Further, "to violate §101, the claimed device must be totally incapable of achieving a useful result." *Juicy whip Inc. v. Orange Bang Inc., 51* U.S.P.Q. 2d 1700 (Fed. Cir. 1999), *citing Brooktree corp. v. Advanced Micro devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992). Therefore, the Examiner's interpretation that, patentability precludes any further experimentation is incorrect.

Moreover, the SVP assay is an *in vitro* assay for identifying potential inflammatory molecules. In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a Examiner decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

The *Fujikawa* case was in the context of utility for pharmaceutical compounds and the principals stated by the Court are applicable in the instant case. Utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility. In this instance, there is "sufficient correlation" between a positive result in the SVP assay (*i.e.,* a

proinflammatory molecule) and utility in disease conditions like cancer and autoimmune disease.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, *i.e.,* there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (Emphasis added).

The *Cross* case is very similar to the present case. Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Appellant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed PRO326 polypeptides without undue experimentation and would not find the disclosure preliminary.

Therefore, Appellants submit that the present application discloses the utility of the subject matter of the instant claims and that one of skill in the art would know exactly how to use the claimed PRO326 polypeptides, for instance, to make polypeptides effective for inducing inflammation and for preparing antibodies to reduce inflammation, without any undue experimentation. The specification provides detailed guidance as to how to identify and make nucleic acids encoding polypeptides having complete amino acid sequence identity to PRO326

polypeptides. The specification also provides ample guidance to allow the skilled artisan to identify those polypeptides which meet the limitations of the claims, found in Example 77 (page 210, lines 22) which describes a dye-based proinflammatory cell infiltration assay in which PRO326 polypeptides induce inflammation, or as "inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal" (page 210, lines 23-24 of the specification). Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed PRO326 polypeptides without undue experimentation. Thus, this rejection of Claims 42-47 and 49-51 should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that the Skin Vascular Permeability assay disclosed in Example 77 of the specification provides at least one asserted specific and substantial patentable utility for the PRO326 polypeptides claimed in Claims 42-47 and 49-51, and that one of ordinary skill in the art would accept this asserted utility as credible and would understand how to make and use the claimed polypeptides. Therefore, Claims 42-47 and 49-51 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. Accordingly, reversal of all the rejections of Claims 42-47, and 49-51 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C27**.

Respectfully submitted,

Date: June 30, 2006

By: (Pampan Guo 43,626)
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